

**REMARKS**

Applicants respectfully request reconsideration of the rejections set forth in the Final Office Action mailed on March 17, 2008.

Claims 1 to 12 were pending in the application. Claims 1-3 and 6-11 were previously withdrawn from consideration, as being drawn to a non-elected invention. Per this amendment, claim 13 has been added.

Claim 13 depends from independent claim 4 and indicates that “phosphorylated Akt is detected.” Support for claim 13 is found throughout the specification, for example, at least at paragraph [0093], which provides that “Akt activity can be detected using a method generally employed in the art, such as the Western blot using an anti-phospho-Akt antibody.” Thus, claim 13 is fully supported by the specification. No new matter has been added.

Upon entry of the present amendment, claims 1, 4-5, and 12-13 will be under consideration.

**Preliminary Matters**

Applicants note with appreciation that the Examiner withdrew the rejection of claim 4 under 35 U.S.C. § 112, second paragraph. *See* Action at page 2.

**Claim Rejections under 35 U.S.C. § 103**

**Claims 4-5**

The Examiner maintained the rejection of claims 4-5 under 35 U.S.C. § 103(a) as allegedly “being unpatentable over Pearson et al. (US 5,591,872, 1997, IDS) in view of Smith et al. (J. Immunol. 2001: 167: 366-374, IDS), Koo et al. (US 2002/0054869, 2002, of record) and Rajan et al. (Am. J. Respir. Cell Mol. Biol. 2000; 23: 304-312, of record).” Action at page 2.

Reiterating the reasoning set forth in the Office Action of September 17, 2007, the Examiner continues to urge that Pearson teaches “a method of selecting inhibitors of the autoinducer molecule, N-(3-oxododecanoyl) homoserine lactone” and Smith teaches “MAP kinases are stimulated by the auto-inducer 3-O-C12-HSL, wherein MAP kinases are known in the art to be involved in apoptosis in view of the teachings of Koo et al. and Rajan et al.” Action at page 5. The Examiner concludes that “the combination of the prior art references appear to teach the same active steps recited in the instant claims, e.g., contacting cells with a test substance in the presence of acylated homoserine lactone and detecting (b) apoptosis.” *Id.*

The Examiner alleges that “with the exception of [the] limitation of determining phosphorylated Akt, the claims do not appear to require, per se, apoptosis and the Akt signaling pathway.” *Id.* at pages 5-6. According to the Examiner, “Applicants have not provided a patentable difference between determining apoptosis as a result of the Raf-MEK-ERK MAP [kinase] signaling pathway and determining apoptosis as a result of the Akt pathway, since all the claims require is determining apoptosis.” *Id.* at page 6.

Applicants respectfully disagree. As set forth in the M.P.E.P., “[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art.” M.P.E.P. § 2143.03 (quoting *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)). Here, the Examiner has overlooked an express claim element. Specifically, the Examiner has not recognized the limitation that the apoptosis and caspase activity are modulated by Akt. Indeed, contrary to the Examiner’s assertions, the claims do require involvement of the Akt pathway. As correctly noted by the Examiner, step (ii)(a) of claim 4 recites “detecting . . . phosphorylated Akt.” More to the point, steps (ii)(b) and (ii)(c) of claim 4 recite “detecting . . . (b) apoptosis, or

caspase activity, **wherein the apoptosis or caspase activity is modulated by Akt**” (emphasis added). Thus, claim 4(ii)(b) requires that the apoptosis involves Akt.

While the Examiner alleged here that the claims do not require the Akt pathway, the Examiner appears to contradict this conclusion later in the Office Action. For example, at page 6, the Examiner acknowledges that “Pearson does not explicitly teach the method comprising culturing animal cells with the test agent and acylated homoserine lactone and **detecting the inhibition of Akt by detecting apoptosis or caspase activity**” (emphasis added). This statement implies that the Examiner recognizes that the claimed apoptosis does require involvement of Akt. Applicants respectfully request that the Examiner clarify this statement.

Further, the Examiner correctly “acknowledges and does not dispute Applicants[’] assertions that the cited combination is silent on the Akt pathway.” *Id.* Relying on *In re Kahn*, however, the Examiner asserts that “[i]t is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by the applicant.”

Applicants respectfully traverse because *In re Kahn* is fundamentally distinguishable from the instant case. For example, *In re Kahn* involved a patent application directed to a mechanical device, specifically, a voice synthesizer. Here, the instant application is drawn to complex biological processes. In addition, Kahn did not dispute that each element of his claims could be found in the prior art documents cited by the Examiner. *See In re Kahn* 441 F.3d at 988. Rather, Kahn asserted that the Board lacked substantial evidence for motivation to combine the cited documents and that the Board should have given more weight to his asserted “secondary considerations,” i.e., “long-felt, but unresolved need.” *See id.* at pages 984-85. Here, as noted above, Applicants and the Examiner agree that the cited art is silent regarding the

Akt pathway, an express limitation of the claims. Thus, *In re Kahn* significantly differs from the instant case.

The Examiner also states that “one of ordinary skill in the art would have [a] reasonable expectation of success that by using MAP kinase as the gene stimulated by 3-O-C12-HSL and determining apoptosis in the method taught by Person et al. in view of the teachings of Koo et al. and Rajan et al., one would achieve an inhibitor of 3-O-C12-HSL.” Action at page 5.

Applicants respectfully disagree. The link between acylated homoserine lactone and inhibition of the Akt was unknown prior the Applicants’ studies. As set forth in the specification, “[b]oth the facts that acylated homoserine lactone inhibits the activities of Akt in animal cells and further induces apoptosis in animals cells have been completely unknown.” Specification at paragraph [0015]. In light of the extremely complex nature of signal transduction pathways, one skilled in the art could not reasonably expect that involvement of the ERK signal transduction pathway or the TNF $\alpha$  production pathway, as discussed below, would have any affect on the Akt pathway.

In fact, acylated homoserine lactone has the opposite affect on ERK, p38, and JNK compared to its affect on Akt. As described in Example 2 at page 10, “acylated homoserine lactone promotes the activation[] of ERK, p38, and JNK, while inhibiting the activity of Akt.” The inhibition of Akt, as opposed to the activation of ERK, mediates acylated homoserine lactone-induced apoptosis. Specifically, Example 1 at pages 9-10 shows that N-(3-oxododecanoyl)-L-homoserine lactone (“HSL”) “significantly decreases Akt activity in PECs” and induces apoptosis. Specification at paragraph [0135]. Example 7 at page 12 shows that ERK is not involved in that apoptosis. As described in Example 7, cells were pretreated with PD98059 to block the ERK pathway and then cultured in the presence of HSL. In the absence of

the ERK pathway inhibitor, HSL induced apoptosis. If HSL-induced apoptosis had been mediated by ERK, then the ERK pathway inhibitor would have increased viability. However, the Example shows that “no effect by pretreatment with PD98059 on viability was observed.” Specification at paragraph [0159]. While ERK is activated by HSL, the ERK signal transduction pathway does not appear to be involved in HSL-induced apoptosis. Thus, Pearson, Koo and Rajan do not provide a reasonable expectation of success.

Accordingly, the cited references do not render obvious the instant claims. For at least those reasons, Applicants respectfully request withdrawal of the rejection.

Claims 4-5 and 12

The Examiner maintained the rejection of claims 4-5 and 12 under 35 U.S.C. § 103(a) as allegedly “being unpatentable over Pearson et al. (US 5,591,872, 1997, IDS) in view of Telford et al. (Infection and Immunity, 1998; 36-42, of record) and Maianski et al. (Blood, 2002; 101: 1987-1995, prepublished online as Blood First Edition Paper, October 10, 2002, of record).” Action at page 6. The Examiner concludes that one would be motivated to “culture a test substance in the presence of N-3-oxodocecanoyl homoserine lactone as taught by Pearson et al. in an animal cell such as a neutrophil and to identify an inhibitor of N-3-oxodocecanoyl homoserine lactone by detecting apoptosis or caspase[] activity in view of the teachings of Telford et al. and Maianski et al.” because “Telford et al. teaches that 3-O-C12-HSL inhibits TNF- $\alpha$  production which is well known in the art to be involved in apoptosis via the activation of caspases as taught by Maianski et al.” *Id.* at pages 6-7. The Examiner also stated that:

[O]ne of skill in the art would have a reasonable expectation of success that by culturing a test substance in the presence of N-3-oxodocecanoyl homoserine lactone as taught by Pearson et al. in an animal cell such as a neutrophil and to identify an inhibitor of N-3-oxodocecanoyl homoserine lactone by detecting apoptosis or

caspase activity in view of the teachings of Telford et al. and Maianski et al., one would achieve an effective method of identifying a suitable inhibitor for the treatment of a immuno-compromised host infected by *P. aeruginosa*.

*Id.* at page 7.

Applicants respectfully disagree for the reasons described above in the response to the rejection over Pearson in view of Smith, Koo, and Rajan. Specifically, the claims require involvement of the Akt pathway and each of Pearson, Telford, or Maianski is totally silent on the Akt signal transduction pathway. Moreover, the secondary references relate to TNF $\alpha$  and apoptosis and do not even connect the ability of a cell to produce TNF $\alpha$  with the Akt pathway. Furthermore, the teachings of Pearson in view of Telford and Maianski do not provide a reasonable expectation of success for a “method of screening for a substance that inhibits acylated homoserine lactone, comprising . . . detecting one or more of . . . (b) apoptosis, or (c) caspase activity, wherein the apoptosis or caspase activity is modulated by Akt and wherein decreased apoptosis or decreased caspase activity reflects inhibition of acylated homoserine lactone.” Regardless of any effect of HSL on TNF $\alpha$  production, the references do not tie TNF $\alpha$  production to Akt. Thus, this combination of references simply cannot provide any teaching or suggestion of the Akt pathway. Accordingly, Applicants respectfully request withdrawal of the rejection.

### **CONCLUSION**

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 1,4-5, and 12-13 in condition for allowance.

It is respectfully submitted that the entering of the Amendment would allow the Applicants to reply to the final rejections and place the application in condition for allowance.

Finally, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

If the Examiner does not find the claims allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6607 to set up an interview.

Please grant any further extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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